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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/787,506	02/26/2004	Darwin J. Prockop	57616-5001-03	4991

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
02/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/787,506	PROCKOP ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-85* is/are rejected.

7)☒ Claim(s) *70 and 79* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 25, 2007 that includes a response to the final office action dated August 3, 2007, has been entered. No claims were amended and no claims cancelled. Claims 78-85 have been newly added. Accordingly, claims 55-85 are pending in the application and under current examination.

Response & New Claim Objections

Claim 70 stands objected to as being a substantial duplicate of claim 56. The objection set forth on p. 2 of the previous office action dated August 3, 2007 is maintained for claim 70, and further applied to newly added claim 79 for reasons of record.

As Applicants' response has deferred the issue until claim 56 is deemed allowable, the objection is maintained for claim 70 and further applied to claim 79.

Response & New Claim Rejections - 35 USC § 112 - Lack of Enablement

Applicants' claim amendments have necessitated the following new ground of rejection.

Claims 55-77 stand rejected under 35 U.S.C. §112, first paragraph, because the specification is not enabling for the claimed invention. The rejection set forth on pp. 2-7 of the previous office action dated August 3, 2007 is maintained for claims 55-77, and further applied to new claims 78-85, for reasons of record.

Applicants traverse the grounds for rejection, stating that embodiments of the presently claimed subject matter are directed to methods for generating, regenerating, or repairing a blood vessel in a mammal, and methods of treating a disease, disorder or condition characterized by a defect in a blood vessel, the methods comprising administering culture expanded autologous or allogeneic bone marrow stromal cells (MSCs) to the mammal, wherein the cells differentiate into

cells of a blood vessel in said mammal. Applicants argue that the specification teaches a person skilled in the arts how to make and use the presently claimed subject matter without undue experimentation; and following systemic administration, a person skilled in the art can therefore use the guidance as provided in the specification and the art to routinely demonstrate whether MSCs differentiate into a cell of a blood vessel, and thereby generate or repair a blood vessel as recited in the claims. Applicants further argue that the present specification contradicts earlier reports indicating that MSCs did not have features characteristic of endothelial cells. Instead, the specification shows that cultured MSCs can serve as stem-cell-like precursors of mesenchymal tissues, which a person skilled in the art knows to include blood vessel tissues and the cells therein, such as endothelial cells. A person skilled in the art also knows that endothelial cells of the blood vessel are central to neovascularization, such as in angiogenesis; and a person skilled in the art understands that the introduction of MSCs, which may differentiate to endothelial cells, may be synonymous with generating a blood vessel as claimed. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it should note that neovascularization is a process distinct from that of angiogenesis. Neovascularization is the formation of microvascular networks, involving capillary formation, that is primarily a combination of endothelium and connective tissue. Angiogenesis is the process involving outgrowths from pre-existing blood vessels. Further distinct from capillaries are the instantly claimed blood vessels, that would include veins and arteries. These larger blood vessels comprise epithelial cells, endothelial cells, connective tissue, intercellular matrix, vascular smooth muscle cells and nerves that supply the muscular layer. Thus, Applicants' assertion that MSCs that may differentiate to endothelial cells, may be synonymous with generating any blood vessel, are incorrect.

As previously indicated, the invention claimed by Applicants, broadly encompassing methods of administering systemically or intraperitoneally, a mixed population of culture expanded autologous, allogeneic or syngeneic bone marrow stromal cells wherein the cells differentiate into any of various cell types, thus generating, or repairing any type of blood vessel (including major veins and arteries) in a mammal, in a tissue specific manner or treating any disease that may be associated with a vascular disorder, was not considered either predictable or well-established either at the time of the instant invention or in post-filing literature.

Furthermore, the absence of working examples or an actual reduction to practice in Applicants' disclosure were additional consideration in the analysis of *Wands* factors in establishing an enabled disclosure for the claimed methods of the invention.

As previously stated, the issue is not the ability of MSCs to differentiate into cardiomyocytes and endothelial cells, but whether the administration of a mixed population of stromal cells can generate any type of blood vessel in appropriate sites in a controlled manner, or repair and treat any type of blood vessel in mammals suffering from numerous diseases, disorders or conditions, following their systemic or intraperitoneal administration, as instantly claimed. The instant specification teaches that the invention is "based upon the discovery that stromal cells introduced into patients by the bloodstream, develop into bone cartilage and lung". Additionally stating: "Similarly, it is believed that stromal cells will also develop into cells of the dermis, blood vessels, heart and kidneys, or throw off daughter cells that will do so." (page 8, line 14-29). As indicated in the previous office actions: "it would require undue experimentation to demonstrate that systemic or intraperitoneal administration of stromal cells would result in the proper differentiation and generation or repair of blood vessels at the site where said blood vessels are required, and not at undesired sites, for the methods of the instant application", because systemic administration of MSCs would result in the dilution of said cells in the animal and would further introduce stem cells to undesired locations wherein subsequent differentiation of the cells into various different lineages could complicate, rather treat a disease state.

Applicants disagree with the foregoing, arguing that the basis for the rejection of the rejection is improper, because the Examiner relies too heavily on post-filing references that arguably should not even be part of the record. However, as previously indicated, the prior art is silent on the ability of a mixed population of bone marrow stromal cells to generate any type of blood vessel and treat any disease, disorder or condition characterized by any defect in any blood vessel. Further, If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993). Thus as the teachings of the post-filing art of record demonstrate unpredictability and the requirement for further experimentation regarding the instantly claimed invention, such teachings should be considered as part of the record.

With regard to the reference of Nagaya et al., Applicants argue that the authors demonstrate the administration and migration of a relatively low number of MSCs to the target organ induces both angiogenesis and myogenesis, and improves clinical outcome, and make passing reference to a concern about the use of "mixed" cell populations. Additionally arguing, there are no grounds to assert that the presently claimed MSCs are any more "mixed" than the cells reported in Nagaya et al., despite the noted presence of a "few" adipocytes and macrophages. Nagaya et al. therefore contains nothing in either the results or the discussion that rationally equates to a statement that it is not possible to generate blood vessels or treat vascular diseases by administering marrow stromal cells as claimed. Such is not found persuasive.

As previously indicated, Nagaya's caution that "the limitation of this study is that the cell population may be mixed, rather than limited to MSCs" is highly relevant in view of Applicants' disclosure, because the instant specification notes that donor cells from marrow are partially enriched for mesenchymal precursors (lines 24-25, p. 31), and that most of the cells were fibroblast-like, but a few macrophages and adipocytes were also seen (lines 8-10, p 32). Thus, the cultured stromal cells of the instant invention as demonstrated by the instant disclosure are a partially mixed population of cells, comprising mostly fibroblast-like cells. Further, regarding Nagaya's observations in neovascularization, Nagaya et al. teach that some of the transplanted MSCs were positive for an endothelial cell marker and participated in vessel formation, and that the plasticity of MSCs to transform into endothelial-like cells provides a rationale for their potential role in neovascularization (first and second column, p. H2675). However, as noted above, a contribution to neovascularization is not synonymous with generation of any type of blood vessel as instantly claimed. It is further clear that the post-filing teachings of Nagaya et al. point to the need for further experimentation. As stated in MPEP 2164.05(a), the specification must be enabling as of the filing date. A later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling.

With regard to Zisch et al. and Dzau et al., Applicants argue that Zisch et al. conclude that the "significance of adult EPCs as therapeutic vehicles for ischemic tissue salvage has been validated" (see, e.g., page 424), thus the underlying results hardly qualify as statements that practicing the presently claimed subject matter is not possible.

As previously indicated, the teachings of Zisch et al. were cited to demonstrate the plasticity of the stem cells can result in the cells developing into a number of different cell types, which is important in light of the systemic and intraperitoneal routes of administration of the instant claims, wherein administered MSCs could be transplanted at numerous sites in a mammal, causing potential undesired differentiation that would likely alter the physiological state of the mammal by providing paracrine growth factor/cytokine signals. These potential pitfalls are equally applicable to MSCs and EPCs, especially in view of the instant specification's disclosure that the MSCs introduced into patients by the bloodstream develop into bone cartilage, dermis, heart, kidneys and blood vessels. Zisch et al. further state: "The interaction between the host environment and EPCs has not been well established...the surprising plasticity of primary EPCs to change fate into cardiomyocyte or mesenchymal phenotypes warrants further investigation so that their potential for exploitation in cardiovascular tissue engineering applications can be further appreciated." It is clear therefore that while EPCs hold therapeutic potential, such potential warrants further investigation, even in post-filing art. The problems highlighted by Dzau et al. regarding potential pitfalls with therapeutic use of autologous EPCs were addressed in the previous rejections.

Regarding the reference of Yoon et al., Applicants argue that the potential concerns with heart calcification described in the reference are not likely relevant to methods of generating blood vessel cells in a mammal as presently claimed, because Yoon et al. directly inject whole bone marrow cells into the heart of rats, such that these hearts are directly and immediately populated with an arguably excessive number of foreign cells. In contrast, the presently claimed subject matter focuses on systemic administration, in which the various tissues are exposed to a relatively dilute population of stromal cells. Such is not found persuasive, because the instant claims (nor the instant specification) do not limit the number of bone marrow stromal cells administered to any number, and further, if as Applicants contend, the cells are relatively dilute, then, how effective can such a dilute population of cells be in generating a whole blood vessel, such as a vein or an artery?

Applicants argue that Yoon et al. use whole bone marrow, a heterogeneous, mixture of cells, composed of multipotent progenitor cells, adipocytes, reticulocytes, endothelial cells, fibroblastic cells, and osteoblasts. In contrast, the instant claims recite the use of enriched MSCs;

a person skilled in the art is likely to conclude that administering enriched (i.e., mostly homogenous) MSCs of the present claims will not lead to the problems described in Yoon et al., such as heart calcification.

Such is not found persuasive, because the instant claims do not recite enriched or mostly homogenous cells. Further, the instant specification teaches that donor cells from marrow are partially enriched for mesenchymal precursors (lines 24-25, p. 31), and that most of the cells were fibroblast-like, but a few macrophages and adipocytes were also seen (lines 8-10, p 32). Thus, there is no basis for Applicants' conclusion that administration of a partially enriched population of MSCs would not lead to the problems described in Yoon et al., such as heart calcification. In fact, Yoon et al. specifically state that any BM-derived stem cells could be considered as candidates for the induction of local calcification (second column, p. 3156).

Applicants argue that the Examiner is failing to apply the appropriate legal standard to the method of treatment claims, and even though a rejection under 35 U.S.C. §101 was never formally made of record, enablement rejections under 35 U.S.C. § 112, first paragraph, which are based on an alleged lack of disclosure relating to therapeutic efficacy, are analyzed under the same legal standard as a rejection under 35 U.S.C. § 101. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). Applicants are directed to the response previously submitted, citing, MPEP 2164.07, the requirement of 35 U.S.C. 112, first paragraph as to how to use the invention is different from the utility requirement of 35 U.S.C. 101. For example, if an applicant has claimed a process of treating a certain disease condition with a certain compound and provided a credible basis for asserting that the compound is useful in that regard, but to actually practice the invention as claimed a person skilled in the relevant art would have to engage in an undue amount of experimentation, the claim may be defective under 35 U.S.C. 112, but not 35 U.S.C. 101. In the instant case, no rejection under 35 U.S.C. 101 is of record, as the examiner has determined that the claimed subject matter meets the requirements under 35 U.S.C. 101, and has further not required human testing.

Applicants cite *In re Angstadt*, 537 F.2d 498,503 (CCPA 1976), and state the courts have rejected as too high the application of a "reasonable certainty" standard in determining the enablement of a disclosure, and attempt to apply the same to administration of MSCs will generate a blood vessel or ultimately treat a mammal with a disease, disorder or condition that is

characterized by a defect in a blood vessel. Applicants further argue that neither examples nor reduction to practice are required for enablement.

In response, it should be noted that given the lack of teachings in both the prior art and the post-filing art for the generation of any type of blood vessel and any of the types of cells associated therewith, to treat any vascular disease or disorder, by systemically or intraperitoneally administering a mixed population of unpurified culture expanded bone marrow stromal cells to a mammal, without inappropriate neovascularization or unwanted angiogenesis, or cardiac calcification, would be considered a treatment that is far from "reasonable certainty", given the lack of working examples and guidance in the instant disclosure. It should be further noted that working examples constitute one of the *Wand*s factors relied upon in an enablement analysis.

Moreover, as previously stated, exogenous mobilization of bone marrow with hematopoietic growth factors and other endothelial growth factors may recruit progenitor cells to sites of occult neoplasia, leading to vascularization of dormant tumors. In addition, mobilization could potentially accelerate progression of atherosclerotic plaque by recruiting inflammatory and vascular smooth muscle cell progenitor cells into the plaque, contributing to neointima hyperplasia and transplant arteriopathy, as well as contribution to allograft vasculopathy by promoting neovascularization of the plaque.

Therefore the rejection of claims 55-77 is maintained and further applied to newly added claims 78-85, for reasons of record and the discussion set forth above.

Obviousness Type Double Patenting

Claims 55-77 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 55-70 of copending Application No. 10/423,232. The rejection set forth on pp. 7-8 of the previous office action dated August 3, 2007 is maintained for claims 55-77, and further applied to new claims 78-85, for reasons of record.

Claims 55-77 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-28 of copending Application No. 10/844,235. The rejection set forth on pp. 7-8 of the previous office action dated

August 3, 2007 is maintained for claims 55-77, and further applied to new claims 78-85, for reasons of record.

As Applicants have not addressed the rejections, the rejections are maintained and further applied to newly added claims 78-85

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 6:30 AM-3:30 PM EST pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on **(571) 272-0739**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of

such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at **(800) 786-9199**.

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Examiner, USPTO, AU 1633

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